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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/678,160

10/06/2003

Eli Sprecher

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07/24/2008

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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT

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1632

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/678,160	Applicant(s) SPRECHER ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 7, 17, 22 and 85-99 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 7, 17, 22, 85-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

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| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413) |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08) | 5) ☐ Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Applicants' amendment to the claims filed May 6, 2008 have been received and entered. Applicants have amended claim 1, while claim 2-6, 8-16, 18-21, 23-84 have been cancelled. Applicants have also added claims 93-99.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/06/2008 has been entered.

Restriction/Election

Applicants' election without traverse of Group IV, claims 1, 7, 17 and 22 filed 30 September 2005 in response to Office Action mailed 7 September 2005 was acknowledged and entered. Since the election is made without traverse, the restriction requirement was deemed proper and was made FINAL.

It is noted that claims 2-6, 8-16, 18-21 and 23-84 were withdrawn from further consideration pursuant to 37 CFR §1.142(b) as being drawn to a nonelected invention. However, during the prosecution of this application, it appears that applicants have re introduced claims 92-93 in amendment filed on 8/9/2007 that specifically recited previously withdrawn molecule (antisense and antibody).

Accordingly, claims of group I and II are rejoined along with elected invention of group IV.

Claims 1, 7, 17, 22, 85-99 are under consideration.

Withdrawn-Claim Rejections - 35 U.S.C. §112

Claims 1, 7, 17, 22, 85-92 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 17, 22, 85-98 and 99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance

provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: “[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection.” These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform “undue experimentation” to make and/or use the invention and therefore, applicant’s claims are not enabled.

Claims 1, 7, 17, 22, 85-98 and 99 are broad in scope, encompassing a method of screening molecule that modulates the P-cadherin intended for inducing or inhibiting hair growth. The claims encompass hair growth modulators (i.e., hair growth inhibitor or inducer) intended for either inducing hair growth to treat alopecia of any etiology or inhibiting hair growth for cosmetic purpose in any subject. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

The nature of the claims requires identifying a hair growth inducer or inhibitor based on the knowledge that uses homozygosity mapping in 4 consanguineous families showing presence of the juvenile macular dystrophy (HJMD) gene to 16q22.1. This region harbors CDH3 encoding P-cadherin, which is shown to be expressed in the retinal pigment epithelium and hair follicles. Mutation analysis in all families revealed a common homozygous deletion in exon 8 of CDH3. The specification correlates the molecular etiology of HJMD and implicates cadherin molecule in the pathogenesis of a human hair and retinal disorder (see

para. 27 of the published application). The specification teaches four large consanguineous HJMD families with 11 affected individuals that were born with normal-appearing hair but developed alopecia of the scalp at about 3 months of age. Furthermore, it is disclosed that during puberty, partial re growth of short and sparse hair occurred (Figure 1a) and histological studies showed normal findings except for a reduced ratio of terminal vs. vellus hair follicles (Figure 1 b-c). These affected individuals developed progressive macular degeneration with slight peripheral retinal dystrophy progressively between the ages of 3 to 21 years (Figure. 1d). The specification also teaches homozygosity mapping to identify a 20 cM segment on chromosome 16q22.1 identical by descent in affected individuals of families 1-3 and subsequent haplotype analysis and multipoint linkage analysis using additional polymorphic markers refined the disease gene locus to a 5 cM interval flanked by D16S3085 and D16S3066 (see figure 2a) at marker D16S3025. Three contigs were identified in the high throughput genomic sequences database that contained at least one of the 4 microsatellite markers located within the HJMD critical interval and these contigs harbored at least 45 different genes including CDH3 encoding P-cadherin. Using direct DNA sequencing and restriction fragment analysis, it was determined that all affected individuals were homozygous for the 981delG mutation, and that their parents were carriers of the mutant allele. The 981delG mutation is predicted to result in translation of a truncated protein lacking its cytoplasmic tail and 3 out of 5 extracellular domains (Figure 2f). P-cadherin membranal expression was markedly reduced in patient skin biopsies (Figure 2g), suggesting HJMD is caused by the loss of P-cadherin function due to a frameshift mutation in CDH3. The specification then cites multiple other references to P-cadherin is specifically expressed in a subset of epithelial cells involved in hair shaft growth regulation. Although determination of allele is routine in the art, predictably correlating any allele within a gene with predisposition to alopecia in any human or non-human individual is unpredictable and the specification does not

predictably correlate polymorphisms of the p-cadherin gene with alopecia of different etiology in human or non-human individual. It is generally known that alopecia is probably a multigenetic disorder, the causes of predisposition are many and it may be difficult for all of them to be envisaged exhaustively. The art further teaches that alopecia is not caused by a small number of genes with major effects but rather is governed in which a combination of genetic and environmental factors that results in the final phenotype (see Martinez-Mir et al Journal of Investigative Dermatology Symposium Proceedings (2003) 8, 199–203). In fact, at the time of filing of this application Martinez-Mir asserts that the pathogenetic basis and etiology of Alopecia areata (AA) are largely unknown (see page 199, col. 2, last para.). It can be concluded from the teaching of the specification and prior art that it would be unpredictable to correlate any one mutation in P-cadherin with alopecia, a condition that is multifactorial and multigenic and therefore not caused by just one gene or polymorphism. The specification does not teach any analysis of any non-human individuals. The specification does not teach any analysis of pathogenetic basis and etiology of alopecia caused by other factors. The specification does not provide any guidance on its association with P-cadherin. The specification does not describe how many individuals were selected, for example did the individuals have other disorders that would cause alopecia, such as endocrine disorder or nutritional disorders. The specification does not teach an association of any other mutation with P-cadherin and alopecia and it is not apparent from the lack of guidance provided by the specification which polymorphism would be predictive of alopecia in any other individual (murine, cat, gerbil, dog, monkey, etc) embraced by the breadth of the claim. Although the specification shows a potential relationship in selected sample population to suggest that HJMD is caused by the loss of P-cadherin function due to a frameshift mutation in CDH3, the specification is silent as to which alleles are associated with the alopecia areata or alopecia of different etiology.

The claims are directed to method for identifying a hair growth inducer or inhibitor by identifying a molecule that induces or inhibits P-cadherin and then testing whether the molecule is functional as a hair growth inducer or inhibitor in any subject. Subsequent claims limit the method to include hair growth inducer or inhibitor is for human. In the instant case, the invention describes need for identifying a molecule that modulates hair growth, and, more particularly for inducing hair growth in cases of alopecia and for inhibiting hair growth at locations where hair is unwanted, using modulators of P-cadherin (See specification background on page 2). The discovery in part is based on the fact that mutation analysis of homozygosity mapping in 4 consanguineous families shows a common homozygous deletion in exon 8 of CDH3 encoding P-cadherin, which is expressed in the retinal pigment epithelium and hair follicles. However, it is unpredictable as to whether or not same mutation of P-cadherin exists in other non-human organisms or across other ethnicity of human population , and whether or not detection of a polymorphism in a human sequence would exist in any other organism that would be predictive of the alopecia. Furthermore, there is no evidence on record that p-cadherin is the only gene mutation that contributes to hair loss in these families. The state of art describe that to date, more than 100 mutations affecting mouse skin or hair have been described, although most have been poorly characterized with little or no comparison to human diseases, The 'lanceolate hair' (*lah*) mouse, for example, is characterized by a generalized form of alopecia associated with the breakage of abnormally formed hair shafts (Irvine et al Clin Exp Dermatol. 2001 Jan;26(1):59-71, IDS). Genetic mapping of the *lah* mutation implicated a 5 cM region of mouse chromosome 18.syntenic to human chromosome 18. No human counterpart of this mouse has yet been identified (see page 68, col. 1para. 2). Similarly, the balding (*hal*) mutation of the mouse causes autosomal recessive alopecia and waves of hair shedding, and maps to mouse chromosome 18. No human counterpart of the *hal* phenotype has been identified. Thus, it is apparent that

genetic mapping in one species may not always correlate with other species. This is further supported by, Mummidi et al(The Journal of Biological Chemistry, 2000, 275, 18946-18961) who teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (see page 18949, col. 2, para. 1). et al Clin Exp Dermatol. 2001 Jan; 26(1):59-71, IDS). Thus it is entirely unpredictable as to whether or not any polymorphism, including the specifically claimed polymorphic positions would be associated with hair loss in different gender across different ethnicity of human population and genus of other species. Furthermore, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. The specification describes 4 families that underwent a genetic linkage analysis simulation. Prior to the instant application, Brookes et al emphasize the need to provide improved power and signal-to-noise discrimination, forward genetics efforts need to be scaled towards thousands rather than hundreds of individuals, and ideally these should be very carefully characterized for multiple gross and detailed phenotypes to broaden and optimize the range of tested characteristics (Brookes et al Trends in Molecular Medicine, 2001, 512-516; see page 514, col. 2, para. 1). Post filing art of Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods (see page 476, col.2, last paragraph). Kroese et al teach that a genetic test is shorthand for describing a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be

assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, col.1 , para. 1 and 2). In the instant case, the state of art teaches HJMD families with 11 affected individuals are born with normal-appearing hair but develop alopecia of the scalp at about 3 months of age. These affected individuals developed progressive macular degeneration with slight peripheral retinal dystrophy progressively between the ages of 3 to 21 years (Figure. 1d). There is no evidence on record that loss of hair observed in this specific population measures with 95% confidence intervals across the population. Kroese et al teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, col.2 , last para.). Additional post filing art reveals that most gene association studies are typically wrong. This is supported by the references by Ionnidis (Plost Med, 2005, 2(8):124) and Hattersley et al (Lancet, 2005, 366, page 1315-1323) which emphasizes the importance of sample size in an association study (see page 1318, col. 2, para. 1). Hattersley et al further emphasizes the need for greater stringency in the association studies in order to prove a given association and suggest a p value of 5×10^{-8} , however arguments from Bayesian perspective suggest that 5×10^{-5} should be sufficient to constrain the false discovery rate. Hegele (Arterioscler. Thromb. Vasc. Biol. 2002; 22; 1058-1061) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (page 1058, col. 2, lines 24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (page 1060, table), and includes choosing an appropriate significance threshold and replication of results in independent samples. Additionally, Hegele teaches the desirability of a likely functional consequence

predicted by a known or putative functional domain. Thus, in absence of any absolute reference value for a gene expression or gene expression product derived from a population of different ethnicity and age, it is unpredictable as to whether or not any level or type of modulation of P-cadherin can in fact be indicative of hair growth. Furthermore, Martinez-Mir et al (Journal of Investigative Dermatology Symposium Proceedings (2003) 8, 199–203) teaches that several causes of alopecia in humans stemming from genetic disorders, endocrine disorders, environmental, as well as other miscellaneous disorders (supra). It is relevant to point out that OMIM lists more than 300 genetic conditions which have hair abnormalities as a component feature, indicates that hair structure and hair follicle morphogenesis, differentiation, proliferation, cycling and maintenance are highly complex biological systems subject to the influence of many genes. In fact it is estimated that more than 100 genes are expressed in hair (see Irvine et al. Clin Exp Dermatol. 2001 Jan;26(1):59-71, IDS, page 59, col. 2, para. 2), while P-cadherin levels are modulated in variety of unrelated conditions (see Yagi et al Gene and Development, 2000, 14, 1169-1180, IDS) . It is reasonable to assert that the states of art clearly suggest that hair loss disorder of different pathology and etiologies involves different and distinct mechanisms that are presently not completely elucidated and modulation in any function of P-cadherin would not be specific to screen molecule for hair growth or hair loss in cosmetic field. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

The specification fails to provide guidance with regard to association of any specific mutation in the P-cadherin gene with hair loss (alopecia) of different etiology and pathology in different species and gender. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for the polymorphism to determine if in fact there was either an association between the polymorphism an individuals and alopecia and to

determine if P-cadherin was involved with hair loss (alopecia). The results of such a study are unpredictable as evidence by the state of the art and the teachings in the specification. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any alopecia. Given the lack of guidance provided by the specification, it would have required undue experimentation for one of skill in art to practice the method as claimed for identifying molecule the modulate P-cadherin and then testing said molecule as hair growth inducer or inhibitor without reasonable expectation of success.

In conclusion, in view of breadth of the claims and absence of a strong showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions. An artisan of skill would have to perform undue experimentation to practice the method as claimed because the art of screening molecule intended for inducing or inhibiting hair growth was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 22, 92, 94, 97 and 99 are rejected under 35 U.S.C. 102(b) as being anticipated by Sprecher et al (Nature Genetics, 2001, 29, 134-136, online published on 9/4/2001, IDS).

Claim Interpretation: Instant rejection is applied to the extent rejection applies to a method of identifying agent that inhibits P-cadherin and testing said agent in a model to determine if it is functional as hair growth inhibitor. As recited these claim merely require testing a molecule that may or may not have intended biological effect. The rejection is applied to the extent claims read on an effect on hair follicle of skin of a 13 day old mouse embryo and not to a method to identify molecule that is functional as hair growth inhibitor or inducer for any subject.

Regarding Claims 17, 22, 92 and 94, Sprecher et al identify P-Cadherin antibody and then test P-Cadherin or E-cadherin antibody on the fresh frozen skin biopsies obtained from a patient and a control sample. Sprecher teaches that P-cadherin is expressed in a subset of epithelial cells involved in hair-shaft growth regulation in the hair follicle (see page 135, col. 3, para. 1). Thus, inhibition of P-cadherin expression by any test agent would imply that it would inhibit hair-shaft growth meeting the limitation of claim 17. As recited claim 17, require testing of agent that in functional as hair growth inhibitor, which is clearly taught by the cited reference. Since instant applicants do not claim any specific polypeptide, a monoclonal antibody is considered a peptide molecule wherein the peptide being a monoclonal antibody specific to P-cadherin specifically that inhibits P-cadherin.

With respect to claims 97 and 99, Sprecher et al disclose inhibition of P-cadherin expression that is determined by microscopic examination of skin tissue in the mixtures of P-cadherin specific and E-Cadherin specific antibodies that is assessed by immuno fluorescence meeting the limitation of claims 97 and 99 (see figure 2).

Accordingly, Sprecher et al anticipate claims 17, 22, 92, 94, 97 and 99.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Blaschuk et al (US 7063842, dated 6/20/2006) teach modulating the adhesion of cadherin-expressing cells including P-cadherin.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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